

CENTRAL FAX CENTER

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AMENDMENTS TO THE CLAIMS

1. **(Withdrawn)** A method for inducing an immune response against a polypeptide antigen in an animal, including a human being, said polypeptide antigen being weakly immunogenic or non-immunogenic in the animal, the method comprising effecting simultaneous presentation by antigen presenting cells (APCs) of the animal's immune system of an immunogenically effective amount of

- 1) at least one CTL epitope derived from the polypeptide antigen and/or at least one B-cell epitope derived from the cell-associated polypeptide antigen, and
- 2) at least one first T helper cell epitope (T_H epitope) which is foreign to the animal.

2. **(Withdrawn)** A method for down-regulating a cell-associated polypeptide antigen in an animal, including a human being, said polypeptide antigen being weakly immunogenic or non-immunogenic in the animal, by inducing a specific cytotoxic T-lymphocyte (CTL) response against cells carrying the cell-associated polypeptide antigen on their surface or harbouring the cell-associated polypeptide antigen in their intracellular compartment, the method comprising effecting, in the animal, simultaneous presentation by a suitable antigen presenting cell (APC) of

- 1) at least one CTL epitope derived from the cell-associated polypeptide antigen, and
- 2) at least one first T-helper lymphocyte (T_H) epitope which is foreign to the animal.

3. **(Withdrawn)** The method according to claim 1, wherein said at least one CTL epitope when presented is associated with an MHC Class I molecule on the surface of the APC and/or wherein said at least one first foreign T_H epitope when presented is associated with an MHC Class II molecule on the surface of the APC.

4. **(Withdrawn)** The method according to claim 1, wherein the APC is a dendritic cell or a macrophage.

5. **(Withdrawn)** The method according to claim 1, wherein the polypeptide antigen is selected from a tumour-associated polypeptide antigen, a self-protein, a viral polypeptide antigen, and a polypeptide antigen derived from an intracellular parasite or bacterium.

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6. **(Withdrawn)** The method according to claim 1, wherein presentation by the APC of the CTL epitope and the first foreign T_H epitope is effected by presenting the animal's immune system with at least one first analogue of the polypeptide antigen, said first analogue comprising a variation of the amino acid sequence of the polypeptide antigen, said variation containing at least the CTL epitope and the first foreign T_H epitope.

7. **(Withdrawn)** The method according to claim 6, wherein the at least first analogue contains a substantial fraction of known and predicted CTL epitopes of the cell-associated polypeptide antigen.

8. **(Withdrawn)** The method according to claim 7, wherein the substantial fraction of known and predicted CTL epitopes in the amino acid sequence of the analogue are recognized by at least 90% of the MHC-I haplotypes recognizing all known and predicted CTL epitopes in the cell-associated polypeptide antigen.

9. **(Withdrawn)** The method according to claim 6, wherein substantially all known CTL epitopes of the cell-associated polypeptide antigen are present in the analogue and/or wherein substantially all predicted CTL epitopes of the cell-associated polypeptide antigen are present in the at least first analogue.

10. **(Withdrawn)** The method according to claim 6, wherein the at least one first analogue further comprises a part consisting of a modification of the structure of the cell-associated polypeptide antigen, said modification having as a result that immunization of the animal with the first analogue induces production of antibodies in the animal against the cell-associated polypeptide antigen.

11. **(Withdrawn)** The method according to claim 1, which comprises effecting presentation to the animal's immune system of an immunogenically effective amount of at least one second analogue of the polypeptide antigen, said second analogue containing a modification of the structure of the polypeptide antigen, said modification having as a result

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that immunization of the animal with the second analogue induces production of antibodies against the cell-associated polypeptide antigen.

12. **(Withdrawn)** The method according to claim 11, wherein the modification comprises that at least one second foreign T_H epitope is included in the second analogue.

13. **(Withdrawn)** The method according to claim 6, wherein the first and/or second analogue(s) comprise(s) a substantial fraction of the cell-associated polypeptide antigen's B-cell epitopes.

14. **(Withdrawn)** The method according to claim 6, wherein the variation and/or modification involves amino acid substitution and/or deletion and/or insertion and/or addition.

15. **(Withdrawn)** The method according to claim 6, wherein the variation and/or modification comprises that

- at least one first moiety is included in the first and/or second analogue(s), said first moiety effecting targeting of the analogue to an antigen presenting cell (APC), and/or
- at least one second moiety is included in the first and/or second analogue(s), said second moiety stimulating the immune system, and/or
- at least one third moiety is included in the first and/or second analogue(s), said third moiety optimizing presentation of the analogue to the immune system.

16. **(Withdrawn)** The method according to claim 6, wherein the variation and/or modification includes duplication of at least one B-cell epitope or of at least one CTL epitope of the cell-associated polypeptide antigen.

17. **(Withdrawn)** The method according to claim 6, wherein the variation and/or modification includes introduction of a hapten.

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18. **(Withdrawn)** The method according to claim 1, wherein the first and/or second foreign T_H epitope(s) is/are immunodominant.

19. **(Withdrawn)** The method according to claim 1, wherein the first and/or second foreign T_H epitope(s) is/are promiscuous.

20. **(Withdrawn)** The method according to claim 12, wherein the first and/or second foreign T_H epitope(s) is/are selected from a natural T_H epitope and an artificial MHC-II binding peptide sequence.

21. **(Withdrawn)** The method according to claim 20, wherein the natural T_H epitope is selected from a Tetanus toxoid epitope such as P2 or P30, a diphtheria toxoid epitope, an influenza virus hemagglutinin epitope, and a *P. falciparum* CS epitope.

22. **(Withdrawn)** The method according to claim 12, wherein the first and/or second T_H epitopes and/or first and/or second and/or third moieties are present in the form of

- side groups attached covalently or non-covalently to suitable chemical groups in the amino acid sequence of the cell-associated polypeptide antigen or a subsequence thereof, and/or
- fusion partners to the amino acid sequence derived from the cell-associated polypeptide antigen.

23. **(Withdrawn)** The method according to claim 22, wherein the first moiety is a substantially specific binding partner for an APC specific surface antigen such as a carbohydrate for which there is a receptor on the APC, e.g. mannan or mannose.

24. **(Withdrawn)** The method according to claim 15, wherein the second moiety is a cytokine selected from interferon γ (IFN- γ), Flt3L, interleukin 1 (IL-1), interleukin 2 (IL-2), interleukin 4 (IL-4), interleukin 6 (IL-6), interleukin 12 (IL-12), interleukin 13 (IL-13),

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interleukin 15 (IL-15), and granulocyte-macrophage colony stimulating factor (GM-CSF), or an effective part thereof; a heat-shock protein selected from HSP70, HSP90, HSC70, GRP94, and calreticulin (CRT), or an effective part thereof; or a hormone.

25. **(Withdrawn)** The method according to claim 15, wherein the third moiety is a lipid such as a palmitoyl group, a myristyl group, a farnesyl group, a geranyl-geranyl group, a GPI-anchor, and an N-acyl diglyceride group.

26. **(Withdrawn)** The method according to claim 6, wherein the first and/or second analogue(s) has/have substantially the overall tertiary structure of the cell-associated polypeptide antigen.

27. **(Withdrawn)** The method according to claim 6, wherein presentation by the APC is effected by administering, to the animal, an immunogenically effective amount of the at least one first analogue.

28. **(Withdrawn)** The method according to claim 27, wherein is also administered an immunologically effective amount of the at least one second analogue.

29. **(Withdrawn)** The method according to claim 27, wherein said at least one first and/or second analogue(s) is/are formulated together with a pharmaceutically and immunologically acceptable carrier and/or vehicle and, optionally an adjuvant.

30. **(Withdrawn)** The method according to claim 29, wherein said adjuvant facilitates uptake by APCs, such as dendritic cells, of the at least first and/or second analogues.

31. **(Withdrawn)** The method according to claim 30, wherein the adjuvant is selected from the group consisting of an immune targeting adjuvant; an immune modulating adjuvant such as a toxin, a cytokine, and a mycobacterial derivative; an oil formulation; a polymer; a micelle forming adjuvant; a saponin; an immunostimulating complex matrix

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(ISCOM matrix); a particle; DDA; aluminium adjuvants; DNA adjuvants; -inulin; and an encapsulating adjuvant.

32. **(Withdrawn)** The method according to claim 31, wherein the cytokine is as defined as in claim 24, or an effective part thereof, wherein the toxin is selected from the group consisting of listeriolycin (LLO), Lipid A (MPL, L180.5/RalLPS), and heat-labile enterotoxin, wherein the mycobacterial derivative is selected from the group consisting of muramyl dipeptide, complete Freund's adjuvant, RIBI, and a diester of trehalose such as TDM and TDE, wherein the immune targeting adjuvant is selected from the group consisting of CD40 ligand, CD40 antibodies or specifically binding fragments thereof, mannose, a Fab fragment, and CTLA-4, wherein the oil formulation comprises squalene or incomplete Freund's adjuvant, wherein the polymer is selected from the group consisting of a carbohydrate such as dextran, PEG, starch, mannan, and mannose; a plastic polymer such as; and latex such as latex beads, wherein the saponin is *Quillaja saponaria* saponin, Quill A, and QS21, and wherein the particle comprises latex or dextran.

33. **(Withdrawn)** The method according to claim 27, which includes administration via a route selected from the oral route and the parenteral route such as the intradermal, the subdermal, the intracutaneous, the subcutaneous; the peritoneal, the buccal, the sublinqual, the epidural, the spinal, the anal, and the intracranial routes.

34. **(Withdrawn)** The method according to claim 27, which includes at least one administration a year, such as at least 2, 3, 4, 5, 6, and 12 administrations a year.

35. **(Withdrawn)** The method according to claim 1, wherein presentation is effected by administering, to the animal, a non-pathogenic microorganism or virus which is carrying a nucleic acid fragment encoding and expressing the at least one CTL epitope and the at least one TH epitope.

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36. **(Withdrawn)** The method according to claim 6, wherein presentation is effected by administering, to the animal, a non-pathogenic microorganism or virus which is carrying at least one nucleic acid fragment which encodes and expresses the at least first analogue.

37. **(Withdrawn)** The method according to claim 15, wherein the T_H epitope and/or the first and/or second and/or third moieties are present in the form of fusion partners to the amino acid sequence derived from the cell-associated polypeptide antigen, and wherein presentation is effected by administering, to the animal, a non-pathogenic microorganism or virus which is carrying at least one nucleic acid fragment encoding and expressing the first and/or second analogue.

38. **(Withdrawn)** The method according to claim 11, wherein presentation is effected by administering, to the animal, a non-pathogenic microorganism or virus which is carrying at least one nucleic acid fragment which encodes and expresses the at least second analogue.

39. **(Withdrawn)** The method according to claim 38, wherein the non-pathogenic microorganism or virus is administered once to the animal.

40. **(Withdrawn)** The method according to claim 1, wherein presentation is effected by in vivo introducing, into the APC, at least one nucleic acid fragment which encodes and expresses the at least one CTL epitope and/or the at least one B-cell epitope, and the at least one first foreign T_H epitope.

41. **(Withdrawn)** The method according to claim 6, wherein presentation is effected by in vivo introducing, into the APC, at least one nucleic acid fragment encoding and expressing the first analogue.

42. **(Withdrawn)** The method according to claim 15, wherein the T_H epitope and/or the first and/or second and/or third moieties are present in the form of fusion partners to the amino acid sequence derived from the cell-associated polypeptide antigen, and wherein

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presentation is effected by in vivo introducing, into the APC, at least one nucleic acid fragment encoding and expressing the first and/or second analogue.

43. **(Withdrawn)** The method according to claim 11, which further comprises in vivo introduction, into the APC, of at least one nucleic acid fragment encoding and expressing the second analogue.

44. **(Withdrawn)** The method according to claim 1, wherein presentation is effected by in vivo co-introducing, into the APC, at least two nucleic acid fragments, wherein one encodes and expresses the at least one CTL epitope and wherein another encodes and expresses the at least one first foreign T_H epitope, and wherein the first foreign T_H epitope is as defined in claim 1.

45. **(Withdrawn)** The method according to claim 40, wherein the nucleic acid fragment(s) introduced is/are selected from naked DNA, DNA formulated with charged or uncharged lipids, DNA formulated in liposomes, DNA included in a viral vector, DNA formulated with a transfection-facilitating protein or polypeptide, DNA formulated with a targeting protein or polypeptide, DNA formulated with a targeting carbohydrate, DNA formulated with Calcium precipitating agents, DNA coupled to an inert carrier molecule, and DNA formulated with an adjuvant.

46. **(Withdrawn)** The method according to claim 45, wherein the adjuvant is selected from the group consisting of the adjuvants defined in claim 30.

47. **(Withdrawn)** The method according to claim 40, wherein the mode of administration is as defined in claim 33.

48. **(Withdrawn)** A method for selection of an immunogenic analogue of a cell-associated polypeptide antigen which is weakly immunogenic or non-immunogenic in an animal, said immunogenic analogue being capable of inducing a CTL response in the

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animal against cells displaying an MHC Class I molecule bound to an epitope derived from the cell-associated polypeptide antigen, the method comprising

- a) identifying at least one subsequence of the amino acid sequence of the cell-associated polypeptide antigen which does not contain known or predicted CTL epitopes,
- b) preparing at least one putatively immunogenic analogue of the cell-associated polypeptide antigen by introducing, in the amino acid sequence of the cell-associated polypeptide antigen, at least one T_H epitope foreign to the animal in a position within the at least one subsequence identified in step a), and
- c) selecting the/those analogues prepared in step b) which are verifiably capable of inducing a CTL response in the animal.

49. (Withdrawn) The method according to claim 48, wherein

- 1) the subsequence identified in step a) further does not contain cysteine residues, or, alternatively, wherein the T_H epitope introduced in step b) does not substantially alter the pattern of cystein residues, and/or
- 2) the subsequence identified in step a) further does not contain known or predicted glycosylation sites, or, alternatively, wherein the T_H epitope introduced in step b) does not substantially alter the glycosylation pattern, and/or
- 3) the subsequence identified in step a) contributes significantly to a patophysiological effect exerted by the cell-associated polypeptide antigen, and wherein the introduction in step b) of the foreign T_H epitope reduces or abolishes said patophysiological effect, and/or
- 4) the subsequence identified in step a) is homologous to an amino acid sequence of a different protein antigen of the animal, and wherein the introduction of the T_H epitope in step b) substantially removes the homology, and/or
- 5) introduction in step b) of the foreign T_H epitope results in preservation of a substantial fraction of B-cell epitopes of the cell-associated polypeptide antigen.

50. (Withdrawn) The method according to claim 49, variant 5, wherein the analogue has the overall tertiary structure of the cell-associated polypeptide antigen.

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51. **(Withdrawn)** A method for the preparation of cell producing an analogue of a cell-associated polypeptide antigen, the method comprising introducing, into a vector, a nucleic acid sequence encoding an analogue which has been selected according to the method of claim 48 and transforming a suitable host cell with the vector.

52. **(Withdrawn)** A method for the preparation of an analogue of a cell-associated polypeptide antigen, the method comprising culturing the cell obtained according to the method of claim 51 under conditions facilitating expression of the nucleic acid sequence encoding the cell-associated polypeptide antigen, and recovering the analogue from the culture supernatant or from the cells.

53. **(Withdrawn)** The method according to claim 52 which further comprises the step of purifying the recovered analogue and, optionally subjecting the purified product to artificial post-translational modifications such as refolding, treatment with enzymes, chemical modification, and conjugation.

54. **(Withdrawn)** The method according to claim 1, wherein the weak cell-associated antigen is selected from the group consisting of 5 alpha reductase, α -fetoprotein, AM-1 , APC, APRIL, BAGE, β -catenin, Bcl2, bcr-abl (b3a2), CA-125, CASP-8 / FLICE, Cathepsins, CD19, CD20, CD21, CD23, CD22, CD33, CD35, CD44, CD45, CD46, CD5, CD52, CD55 (791Tgp72), CD59, CDC27, CDK4, CEA, c-myc, Cox-2, DCC, DcR3, E6 / E7, EGFR, EMBP, Ena78, farsyl transferase, FGF8a or FGF8b, FLK-1/KDR, Folic Acid Receptor, G250, GAGE-Family, gastrin 17, Gastrin-releasing hormone (Bombesin), GD2 / GD3 / GM2, GnRH, GnTV, GP1, gp100 / Pmel 17, gp-100-in4, gp15, gp75 / TRP-1, hCG, Heparanase, Her2 / neu, HMTV, Hsp70, hTERT (telomerase), IGFR1, IL-13R, iNOS, Ki 67, KIAA0205, K-ras, H-ras, N-ras, KSA (CO17-1A), LDLR-FUT, MAGE Family (MAGE-1, MAGE-2, MAGE-3, etc), Mammaglobin, MAP17, Melan-A / MART-1, mesothelin, MIC A/B, MT-MMP's, Mox1, Mucin such as MUC-1, MUC-2, MUC-3, and MUC-4 being abberantly glycosylated, MUM-1, NY-ESO-1, Osteonectin, p15, P170 / MDR1, p53, p97 / melanotransferrin, PAI-1, PDGF, Plasminogen (uPA), PRAME, Probasin, Progenipoitin,

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PSA, PSM, RAGE-1, Rb, RCAS1, SART-1, SSX gene family, STAT3, STn (mucin assoc.), TAG-72, TGF- α , TGF- β , Thymosin β 15, TNF- α , TPA, TPI, TRP-2, Tyrosinase, VEGF, ZAG, p16INK4, and Glutathione S-transferase.

55. **(Withdrawn)** The method according to claim 53, wherein the cell-associated polypeptide antigen is human PSM.

56. **(Withdrawn)** The method according to claim 54, wherein the foreign T-cell epitope is introduced in a part of the PSM amino acid sequence defined by SEQ ID NO: 2 positions 16-52 and/or 87-108 and/or 210-230 and/or 269-289 and/or 298-324 and/or 442-465 and/or 488-514 and/or 598-630 and/or 643-662 and/or 672-699.

57. **(Withdrawn)** The method according to claim 55 used in the treatment or amelioration of prostate cancer.

58. **(Withdrawn)** The method according to claim 53, wherein the cell-associated polypeptide antigen is fibroblast growth factor 8b (FGF8b).

59. **(Withdrawn)** The method according to claim 57, where the foreign T-cell epitope is introduced in a part of the FGF8b amino acid sequence defined by SEQ ID NO: 6 positions 1-54 and/or 178-215 and/or 55-58 and/or 63-68 and/or 72-76 and/or 85-91 and/or 95-102 and/or 106-111 and/or 115-120 and/or 128-134 and/or 138-144 and/or 149-154 and/or 158-162 and/or 173-177, and wherein the introduction preferably does not substantially involve amino acids 26-45 and amino acids 186-215.

60. **(Withdrawn)** The method according to claim 58 used in the treatment or amelioration of cancer such as prostate cancer and breast cancer.

61. **(Withdrawn)** The method according to claim 53, wherein the cell-associated polypeptide antigen is Her2.

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62. **(Withdrawn)** The method according to claim 60, wherein the foreign T-cell epitope is introduced in a part of the Her2 amino acid sequence defined by SEQ ID NO: 3 positions 5-25 and/or 59-73 and/or 103-117 and/or 149-163 and/or 210-224 and/or 250-264 and/or 325-339 and/or 369-383 and/or 465-479 and/or 579-593 and/or 632-652 and/or 653-667 and/or 661-675 and/or 695-709 and/or 710-730.

63. **(Withdrawn)** The method according to claim 61 used in the treatment or amelioration of breast cancer.

64. **(Withdrawn)** An analogue of human PSM which is immunogenic in humans, said analogue comprising a substantial part of all known and predicted CTL and B-cell epitopes of PSM and including at least one foreign T_H epitope as defined in claim 18.

65. **(Withdrawn)** The analogue according to claim 63, wherein the at least one foreign T_H epitope is present as an insertion in the PSM amino acid sequence or as a substitution of part of the PSM amino acid sequence or as the result of deletion of part of the PSM amino acid sequence.

66. **(Withdrawn)** The analogue according to claim 64, wherein the foreign T_H epitope is introduced in the positions defined in claim 55.

| 67. **(Canceled)**

| 68. **(Canceled)**

69. **(Currently Amended)** An analogue of human Her2 which is immunogenic in humans, said analogue comprising continuous sequence a substantial part of all known and predicted CTL and B-cell epitopes of the extracellular part of Her2 starting at SEQ ID NO:3 amino acid residue 1 and including at least amino acid residue 654, which is modified with one immunodominant foreign T_H epitope, wherein the at least one foreign

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~~T_H epitope is present as an insertion in the Her2 amino acid sequence or as a substitution of part of the Her2 amino acid sequence or as the result of deletion of part of the Her2 amino acid sequence and wherein the foreign T_H epitope is introduced in a part of the Her2 amino acid sequence defined by SEQ ID NO: 3 at one or more positions selected from the group consisting of amino acid residues 5-25, and/or 59-73, and/or 103-117, and/or 149-163, and/or 210-224, and/or 250-264, and/or 325-339, and/or 369-383, and/or 465-479, and/or 579-593, and/or 632-652, and/or 653-667, and/or 661-675, and/or 695-709, and/or 710-730, wherein said at least one or more foreign T_H epitope is present as an insertion or results from a substitution or a deletion.~~

70. **(Withdrawn)** An analogue of human/murine FGF8b which is immunogenic in humans, said analogue comprising a substantial part of all known and predicted CTL and B-cell epitopes of FGF8b and including at least one foreign T_H epitope as defined in claim 18.

71. **(Withdrawn)** The analogue according to claim 69, wherein the at least one foreign T_H epitope is present as an insertion in the FGF8b amino acid sequence or as a substitution of part of the FGF8b amino acid sequence or as the result of deletion of part of the FGF8b amino acid sequence.

72. **(Withdrawn)** The analogue according to claim 70, wherein the foreign T_H epitope is introduced in the positions defined in claim 58.

73. **(Withdrawn)** An immunogenic composition which comprises, as an effective immunogenic agent the analogue according to claim 64 in admixture with a pharmaceutically and immunologically acceptable carrier or vehicle, and optionally an adjuvant.

74. **(Withdrawn)** A nucleic acid fragment which encodes an analogue according to claim 64.

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75. **(Withdrawn)** A vector carrying the nucleic acid fragment according to claim 73.

76. **(Withdrawn)** The vector according to claim 74 which is capable of autonomous replication.

77. **(Withdrawn)** The vector according to claim 75 which is selected from the group consisting of a plasmid, a phage, a cosmid, a mini-chromosome, and a virus.

78. **(Withdrawn)** The vector according to claim 75, comprising, in the 5'63' direction and in operable linkage, a promoter for driving expression of the nucleic acid fragment according to claim 74, optionally a nucleic acid sequence encoding a leader peptide enabling secretion of or integration into the membrane of the polypeptide fragment, the nucleic acid fragment according to claim 74, and optionally a nucleic acid sequence encoding a terminator.

79. **(Withdrawn)** The vector according to claim 75 which, when introduced into a host cell, is integrated in the host cell genome or is not capable of being integrated in the host cell genome.

80. **(Withdrawn)** A transformed cell carrying the vector of claim 75.

81. **(Withdrawn)** A composition for inducing production of antibodies against PSM, Her2 or FGF8b, the composition comprising

- 1) a nucleic acid fragment according to claim 74 or a vector according to claim 75, and
- 2) a pharmaceutically and immunologically acceptable diluent and/or vehicle and/or adjuvant.

82. **(Withdrawn)** A stable cell line which carries the vector according to claim 75 and which expresses the nucleic acid fragment according to claim 74, and which optionally secretes or carries the analogue according to claim 64 on its surface.

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83. (Withdrawn) A method for the preparation of the cell according to claim 80, the method comprising transforming a host cell with the nucleic acid fragment according to claim 74 or with the vector according to claim 75.

84. (Cancelled)

85. (Cancelled)

86. (Previously Presented) The analogue according to claim 69, wherein the immunodominant foreign T_H epitope is promiscuous.

87. (Cancelled)

88. (Cancelled)

89. (Previously Presented) The analogue according to claim 86, wherein the immunodominant foreign T_H epitope is selected from a natural T_H epitope and an artificial MHC-II binding peptide sequence.

90. (Cancelled)

91. (Cancelled)

92. (Previously Presented) The analogue according to claim 89, wherein the natural T_H epitope is selected from a Tetanus toxoid epitope, a diphtheria toxoid epitope, an influenza virus hemagglutinin epitope, and a P. falciparum CS epitope.

93. (Cancelled)

94. (Cancelled)

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95. (Previously Presented) The analogue according to claim 92, wherein the natural T_H epitope has consists of SEQ ID NO: 12 or SEQ ID NO: 14.